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Temozolomide chemotherapy for patients with newly diagnosed glioblastoma in the CENTRIC EORTC 26071-22072 and CORE trials: Does time of administration matter?

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Abstract

Background. Preclinical work and retrospective studies suggest that temozolomide chemotherapy in glioblastoma may be more effective when administered in the morning rather than the evening. Here we examine the effect of timing in a large cohort of patients in 2 contemporaneous randomized clinical trials.

Methods. We assessed toxicity and survival data in patients with newly diagnosed glioblastoma enrolled in the CENTRIC EORTC 26071-22072 ($n = 545$, MGMT methylated) and CORE ($n = 265$, MGMT unmethylated) trials. We compared the outcome and toxicity of patients who took maintenance (adjuvant) temozolomide (TMZ) either in the morning (TMZ-m), afternoon (TMZ-a) or in the evening (TMZ-e).

Results. In CENTRIC and CORE, $n = 102/260$ (39%) and 50/198 (25%) received TMZ in the morning versus $n = 35/260$ (13%) and 34/198 (17%) in the evening. There was no difference in overall survival (OS) between the TMZ-m and TMZ-e groups (CENTRIC: adjusted mOS 20.6 months (95% confidence interval [CI], 18.4-23.4) TMZ-m vs 21.1 months (95% CI, 18.4-24.5) TMZ-e; adjusted hazard ratio (HR), 0.93 (95% CI, 0.63-1.39); $P = .7$; CORE: adjusted mOS, 10.9 months (95%CI, 9.7-11.8) TMZ-m vs 11.4 months (95%CI, 9.9-12.9) TMZ-e; adjusted HR, 0.87, 95%CI, 0.55-1.38); $P = .6$). The TMZ-m group had a higher proportion of bone marrow toxicity (CENTRIC: TMZ-m 33% vs TMZ-e 11%, $P = .013$, CORE: TMZ-m 24% vs TMZ-e 3%, $P < .01$).

Conclusion. In this post hoc analysis, we found no difference in outcome based on the time of TMZ administration. Bone marrow toxicity might occur more frequently when temozolomide is administered in the morning. Given the limitation to data from deceased patients only, these analyses should be viewed as exploratory only.

Key Points

- Administration time of temozolomide in the maintenance phase of newly diagnosed glioblastoma treatment may not impact survival.
- Bone marrow toxicity might occur less frequently in patients receiving temozolomide in the evening compared to the morning.

Glioblastoma remains one of the most daunting challenges in oncology, characterized by its aggressiveness and limited treatment options. Despite the current standard of care, consisting of maximal safe resection followed by concurrent chemoradiation with temozolomide (TMZ) and up to 6 cycles of maintenance TMZ, only a minority of patients live longer than 2 years.[1]

Chronotherapy is of renewed interest in oncology. Circadian rhythms, regulated by internal biological clocks, intricately govern numerous physiological processes

Importance of the Study

- Chronotherapy for glioblastoma has recently raised significant interest. While preclinical studies and a retrospective study suggested that the timing of temozolomide administration might be associated with outcomes in patients with newly diagnosed glioblastoma, our post hoc analysis of patients enrolled in two large prospective multi-national clinical trials does not provide evidence to support this. Our data may help patient counseling and inform further research efforts.

within the human body, including cellular equilibrium. Disruptions in these rhythmic patterns have been implicated in various pathologies, including cancer. Specifically, the dysregulation of circadian rhythms has not only been closely associated with cancer development and progression,[2] but has also been suggested to affect the efficacy of systemic treatments targeting glioblastoma.[3] The timing of drug administration to synchronize with the patient's circadian rhythm, often referred to as chronotherapy, presents a promising approach to optimize treatment effectiveness.

Recent publications suggest that the exploration of circadian rhythms is a potential avenue to enhance the efficacy of new and current treatments.[3,4] Involvement of the circadian clock in glioblastoma tumorigenesis, namely brain and muscle ARNT-like 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK), exhibit increased expression in glioblastoma and are associated with unfavorable patient outcomes suggesting that the circadian clock may also be a regulator of glioma tumorigenesis.[2] Notably, BMAL1 and CLOCK may play pivotal roles in sustaining glioblastoma stem cells and fostering the development of a pro-tumorigenic tumor microenvironment.[3] These findings suggest that chronotherapy could potentially enhance glioblastoma treatment strategies, including the current chemotherapy regimen with TMZ.

In the EORTC/NCIC 26981-22091/CE.3[1] study protocol, where TMZ was added to radiotherapy and showed prolonged overall survival, administration in the morning was suggested during the maintenance phase. In the current clinical practice, some centers advise evening administration to mitigate gastrointestinal side effects. Given the growing interest in chronotherapy in cancer treatment, particularly in glioblastoma where no effective systemic treatments have been identified since the EORTC-RTOG 26981 trial, exploring the benefits of chronotherapy to enhance the effect of TMZ is becoming increasingly timely.[3] In a retrospective single-center series published in 2021[5] comprising 166 newly diagnosed glioblastoma patients who underwent biopsy or resection followed by concurrent chemoradiation, those treated with TMZ in the morning (TMZ-m) in the maintenance phase of the standard of care exhibited improved overall survival compared to those treated with TMZ in the evening (TMZ-e). This effect was most pronounced among cases with a methylated MGMT promotor and thus a higher predicted sensitivity for TMZ. However, limitations such as patient selection biases are inherent in such retrospective and single-center analyses. A small phase 2 study by the same group demonstrated the feasibility of chronotherapy with TMZ in glioma patients, showing that >95% of 35 glioma patients were compliant with the prescribed administration time.[6]

Here, we undertook an analysis of survival and toxicity outcomes from a comprehensive database encompassing patients enrolled in the CENTRIC EORTC 26071 study[7] and the contemporary similarly designed CORE[8] trial, aiming at comparing TMZ morning to evening administration.

Methods

Patients

The CENTRIC EORTC 26071-22072 study was a multicenter, randomized, open-label, phase III study to assess the effectiveness of combining cilengitide with the standard of care in patients with newly diagnosed glioblastoma with a methylated MGMT promoter.[7] The CORE study was a multicenter, randomized, open-label, controlled, phase II study aimed at determining the safety and effectiveness of 2 different cilengitide regimens when used alongside standard of care for patients with newly identified glioblastoma with an unmethylated MGMT promoter.[8] All patients underwent standard of care, consisting of maximum safe neurosurgical resection followed by combined radiochemotherapy followed by a maintenance phase consisting of up to 6 cycles TMZ chemotherapy. Treatment for all participants was administered in accordance with the respective study protocols, with cilengitide being delivered through intravenous infusions twice a week. There were no requirements on the timing of TMZ in the studies. The primary endpoint of both the CENTRIC EORTC 26071-22072 and CORE studies was not met.[7,8]

For this non-prespecified secondary analyses, interpretation of EU regulations restricted access to patient data who were deceased at the time of database closure (April 1, 2024). As a result, we were able to include 72% of all patients in the CENTRIC study. In contrast, for the CORE study, conducted under U.S. regulations but subject to the same interpretation, we could utilize 75% of all available survival data.

All patients provided written informed consent for participation in the clinical trials, studies were approved by the respective Institutional Review Boards or Ethics committees of the participating institutions. The research protocol for this retrospective analysis was reviewed and approved by the Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands (ethics committee number 23-0150). The study was conducted in accordance with the Declaration of Helsinki.

TMZ administration

As daily TMZ administration during the concomitant chemoradiotherapy is commonly dictated by the time of radiotherapy (per label to be taken approx. 90 min prior to radiotherapy), and, as a result, the timing of TMZ administration varied significantly throughout the radiotherapy treatment, we restricted the analysis to TMZ administration time during the maintenance (adjuvant) treatment phase (5 days every 4 weeks). Administration times were recorded in the eCRF based on patients' drug diaries.

Based on circadian rhythm, the administration time was categorized into three time periods, morning administration (TMZ-m) was defined as 00:00-11:00 AM, afternoon (TMZ-a) as 11.00 AM and 06:00 PM, and evening (TMZ-e) as 06.00:11:59PM. Patients for whom no administration time was recorded were excluded from this analysis. Each patient was categorized into the group with the majority of administration times. If administration times of one single cycle or one day of the cycle were lacking, we assumed that administration times were similar to other cycles or days of the cycle.

Survival

Overall survival (OS) was defined as the interval (days) between the start of maintenance therapy and death for any cause. For patients were still alive at the time of analysis cutoff, no data were provided and those patients could not be included in any analyses. Progression-free survival (PFS), according to the Macdonald criteria, was defined as the interval (days) between start of maintenance therapy and the date of progression (based on the actual tumor assessment date), or death for any cause, whichever came first. The death of a patient without a reported progression was considered as an event on the date of death. Patients who had no post-baseline assessments and did not have an event were censored at the time of randomization (ie, Day 1).

To correct for the missing data from the censored patients, the censoring times were imputed using the prevalence of patients in each administration time group. Specifically, we randomly sampled from a uniform distribution within the interval of the first and last censoring time of each group.

Toxicity

All adverse events (AEs) according to Common Terminology Criteria for Adverse Events version 3.0[9] were evaluated. AEs of special interest were bone marrow failure and nausea, which were evaluated and reported as organ class AEs (gastrointestinal disorders and blood and lymphatic system disorders). Only AEs that started during the maintenance phase were being considered. AEs were evaluated using Pearsons Chi-square tests comparing the number of patient experiencing an AE (of any kind) at least once versus never between the TMZ administration groups. Occurrences denote the total number of times an AEs was documented, regardless of whether it involved the same patient. Additionally, the number of patients for each AE was determined, based on the worst grade experienced by each patient.

Statistical analysis

For continuous variables calculated the number of valid observations (n), 1. Quartile, Median, 3. Quartile and number of missing values (Unknown) were calculated. For visualization histograms, and Kaplan-Meier curves were used. The categorical variables were reported in absolute numbers and percentages, with missing values as a separate category. For the analysis of TMZ administration time only patients with maintenance TMZ and only included the observations during the maintenance phase were included. Kaplan-Meier curves were plotted and median OS and PFS with 95% CI were calculated. Since no randomization was performed for the TMZ administration timing, a multivariable Cox regression model was fitted, including factors such as sex, age, and treatment. This model was used to adjust the survival curves using the direct standardization method.[10,11] from the R package adjusted curves. The adjusted survival curves were visualized, and median OS and PFS with 95% CI were calculated. The HR was calculated based on the multivariate model for the contrast between TMZ-m and TMZ-e. The datasets were analyzed individually.

Results

Data of the 393 deceased patients in the CENTRIC EORTC 26071-22072 trial and 196 deceased patients enrolled in the CORE study were available for the current study. The flow of patients in this study is presented in Figure 1. Patient characteristics are shown in Supplementary Table S1. A total of 260 (CENTRIC) and 154 (CORE) patients had at least 1 TMZ administration captured in the trial database.

Both trials did not show a difference in survival nor toxicity whether patients were treated with or without cilengitide.

In CENTRIC, $n = 102/260$ (39%) received TMZ in the morning and $n = 35/260$ (13%) in the evening. In CORE, 50/154 (35%) patients received TMZ in the morning and 34/154 (22%) in the evening. Notably, almost half of the patients took the TMZ in the afternoon, between 11:00 AM and 06:00 PM (Supplementary Figure S1). Tables 1 and 2 show the characteristics of the patients in the morning, afternoon, and evening groups for CENTRIC and CORE, respectively. Patients that were randomized to the experimental trial arm(s) administered their TMZ more often in the afternoon. There were no other differences significant between these groups.

Survival

In the 393 deceased patients in CENTRIC, the median OS from start of adjuvant therapy was 21.6 months (95% CI: 20.1-23.2) and did not differ between the interventional arm and the control arm (23 vs 21 months, $P = .5$). There was no difference in OS between the groups after

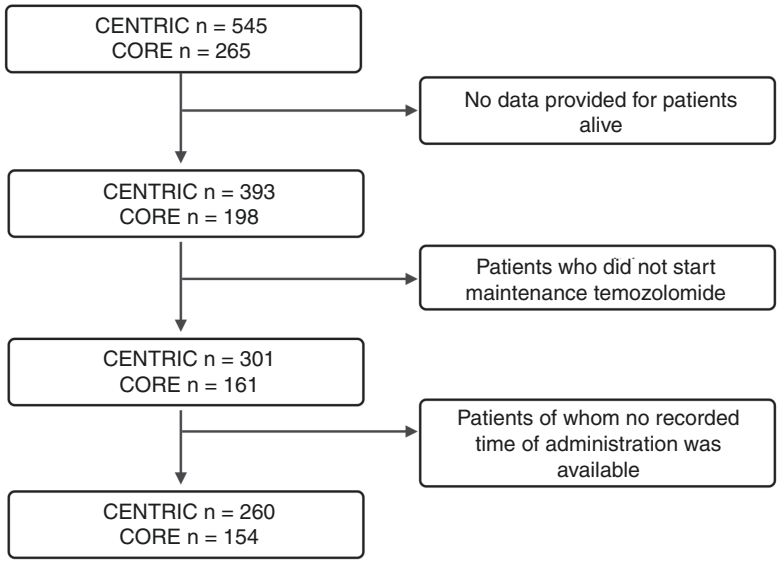

Figure 1. Flow of patients through this study.

adjustment ($n = 260$, adjusted median OS, 20.6 months (95% CI, 18.4-23.4) TMZ-m vs 21.1 months (95% CI, 18.4-24.5) TMZ-e; adjusted HR, 0.93, (95% CI, 0.63-1.39); $P = .7$) (Figure 2A). Accordingly, PFS did not differ between the groups ($n = 216$, adjusted median PFS, 10.7 months (95% CI, 8.3-13.6) TMZ-m vs 9.7 months (95% CI, 7.8-13) TMZ-e; adjusted HR, 1.17 (95% CI, 0.77–1.78); $P = .5$) (Figure 2B). There were no differences in OS or PFS between TMZ-m, TMZ-a and TMZ-e (data not shown).

In the 198 deceased patients in CORE, the median OS was 12.4 months (95% CI: 11.7-13.4) and did not differ between the three arms ($P = .12$). There was no difference in OS between the groups after adjustment ($n = 154$, adjusted median OS, 10.9 months (95% CI, 9.7-11.8) TMZ-m vs 11.4 months (95% CI, 9.9-12.9) TMZ-e; adjusted HR, 0.87, (95% CI, 0.55-1.38); $P = .6$) (Figure 2C). There was a longer PFS in patients who administer their TMZ in the morning as compared to those who administer it in the evening, that just reached statistical significance ($n = 132$, adjusted median PFS, 5.3 months (95% CI, 4.8-6.7) TMZ-m vs 3.6 months (95% CI, 3.2-5.1) TMZ-e; adjusted HR, 1.75 (95% CI, 1.01–3.01); $P = .046$). (Figure 2D). Supplementary Figure S2 shows the results of the unadjusted analyses. There were no differences in OS or PFS between TMZ-m, TMZ-a and TMZ-e (Figure 2 and Supplementary Figure S2).

After imputation, the survival curves for both trials remained largely consistent with the original results, suggesting that the imputed data does not significantly alter the interpretation of our findings (Supplementary Figures S3 and S4).

Toxicity

There was no difference in general toxicity profiles between the TMZ-m and TMZ-e groups (any grade AE, CENTRIC: TMZ-m 67/102 (66%) vs TMZ-e 24/35 (69%), $P = .8$, CORE: TMZ-m 23/50 (46%) vs TMZ-e 14/34 (41%), $P = .7$, Table 3). The TMZ-m group had a higher proportion of patients with any grade of bone marrow toxicity (evaluated as AEs of organ class blood and lymphatic system disorder, see *Methods* section), compared to the TMZ-e group (CENTRIC: TMZ-m 34/102 (33%) vs TMZ-e 4/35 (11%), $P = .013$, CORE: TMZ-m 12/50 (24%) vs TMZ-e 1/34 (3%), $P < .01$). This was also true for grade 3 or higher bone marrow toxicity in CENTRIC (TMZ-m 19/102 (19%) vs TMZ-e 4/35 (11%), $P = .03$), but not in CORE, where patients numbers were small (TMZ-m 3/50 (6%) vs TMZ-e 1/34 (3%), $P = .5$) Any grade of gastrointestinal disorders occurred more often in patients taking the TMZ in the evening in CENTRIC (TMZ-m 24/102 (24%) vs TMZ-e 15/35 (43%), $P = .029$), but not in CORE (TMZ-m 12/50 (24%) vs TMZ-e 7/34 (21%), $P = .7$) (Table 3, Supplementary Tables S2 and S3). There were no differences in toxicity between TMZ-m, TMZ-a, and TMZ-E.

Discussion

In this post hoc analysis of two large randomized clinical trials, there was no indication that time of administration of maintenance TMZ matters for the survival of patients with newly diagnosed glioblastoma.

Our results differ from those of a retrospective single-center study[5] that observed a longer overall survival with morning administration of TMZ. Several factors may contribute to the discrepancy between their findings and our results. We were able to analyze a much larger and prospectively collected patient number, in a well-defined multicenter population, which increased the reproducibility. Single-center and retrospective case series often have biased patient populations. In the retrospective study, there was a group of physicians who prescribed TMZ in the morning, while a single physician prescribed it in the evening. One could argue that patients were not

Table 1. Patient Characteristics of the Morning, Afternoon, and Evening Groups in CENTRIC According to the Categorization of TMZ Administration Times for the Restricted Dataset of Deceased Patients

Characteristic	Morning, *N* = 102[a]	Afternoon, *N* = 123[a]	Evening, *N* = 35[a]	*P*-value[b]
Age	59 (52, 64)	58 (51, 63)	57 (51, 64)	0.8
Unknown	32	23	13	
Age group				0.8
<50	23 (23%)	24 (20%)	7 (20%)	
≥65	23 (23%)	28 (23%)	11 (31%)	
50-65	56 (55%)	71 (58%)	17 (49%)	
Sex				0.8
Female	42 (41%)	49 (40%)	16 (46%)	
Male	60 (59%)	74 (60%)	19 (54%)	
ECOG				0.3
0	65 (64%)	73 (59%)	26 (74%)	
1	36 (36%)	50 (41%)	9 (26%)	
Unknown	1	0	0	
RPAGR2				0.8
Class III	19 (19%)	17 (14%)	6 (17%)	
Class IV	62 (61%)	81 (67%)	24 (69%)	
Class V	20 (20%)	23 (19%)	5 (14%)	
Unknown	1	2	0	
MMSE				.6
<27	22 (22%)	27 (22%)	5 (14%)	
≥27	78 (78%)	95 (78%)	30 (86%)	
Unknown	2	1	0	
Steroid (baseline)				.4
No	68 (67%)	72 (59%)	20 (57%)	
Yes	34 (33%)	51 (41%)	15 (43%)	
Extent of surgery				.4
Total resection	40 (40%)	62 (51%)	17 (49%)	
Partial resection	59 (58%)	56 (46%)	17 (49%)	
Biopsy	2 (2.0%)	4 (3.3%)	1 (2.9%)	
Unknown	1	1	0	
Antiepileptics (baseline)				.13
EIAED	20 (20%)	21 (17%)	9 (26%)	
No antiepileptics	34 (34%)	61 (50%)	13 (37%)	
Non-EIAED only	47 (47%)	41 (33%)	13 (37%)	
Unknown	1	0	0	
Treatment				<.001
Cilengitide	30 (29%)	86 (70%)	14 (40%)	
Control	72 (71%)	37 (30%)	21 (60%)	

[a]Median (IQR); *n* (%).
[b]Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test.

randomly assigned to a physician, and that the particular physician might have seen more fragile patients due to unknown factors. Additionally, theirs and our rather arbitrary cutoff times for morning and evening administration were slightly different.

We did not find an association between the time of administration of TMZ and overall survival, but there was a longer progression-free survival in patients with glioblastoma with an unmethylated MGMT promoter who administered the TMZ in the morning after adjusting for baseline

Table 2. Patient Characteristics of the Morning, Afternoon, and Evening Groups in CORE According to the Categorization of TMZ Administration Times for the Restricted Dataset of Deceased Patients

Characteristic	Morning, *N* = 50[a]	Afternoon, *N* = 70[a]	Evening, *N* = 34[a]	*P*-value[b]
Age	53 (47, 59)	56 (49, 62)	57 (51, 62)	.2
Age group				.4
<50	18 (36%)	18 (26%)	7 (21%)	
≥65	4 (8.0%)	12 (17%)	6 (18%)	
0-65	28 (56%)	40 (57%)	21 (62%)	
Sex				.4
Female	22 (44%)	26 (37%)	10 (29%)	
Male	28 (56%)	44 (63%)	24 (71%)	
ECOG				.3
0	26 (52%)	32 (46%)	21 (62%)	
1	24 (48%)	38 (54%)	13 (38%)	
RPAGR2				.076
Class III	9 (18%)	10 (14%)	6 (18%)	
Class IV	37 (76%)	46 (66%)	18 (53%)	
Class V	3 (6.1%)	14 (20%)	10 (29%)	
Unknown	1	0	0	
MMSE				.13
<27	5 (10%)	15 (21%)	9 (26%)	
≥27	45 (90%)	55 (79%)	25 (74%)	
Steroid (baseline)				.4
No	36 (72%)	43 (61%)	20 (59%)	
Yes	14 (28%)	27 (39%)	14 (41%)	
Extent of surgery				.3
Total tumor resection	23 (47%)	43 (61%)	18 (53%)	
Partial tumor resection	24 (49%)	24 (34%)	12 (35%)	
Biopsy	2 (4.1%)	3 (4.3%)	4 (12%)	
Unknown	1	0	0	
Antiepileptics (baseline)				.8
EIAED	10 (20%)	11 (16%)	8 (24%)	
No antiepileptics	22 (44%)	28 (40%)	14 (41%)	
Non-EIAED only	18 (36%)	31 (44%)	12 (35%)	
Treatment				<.001
Control	30 (60%)	9 (13%)	16 (47%)	
Cilengitide (stand.)	11 (22%)	26 (37%)	8 (24%)	
Cilengitide (int.)	9 (18%)	35 (50%)	10 (29%)	

[a]Median (IQR); *n* (%).
[b]Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test.

characteristics. This difference was only present in CORE, which included solely patients whose tumors had an unmethylated MGMT promoter, and not in CENTRIC, where a methylated MGMT promoter was defined as eligibility criterion. Since the general benefit of TMZ is largely restricted to patients with glioblastoma with a methylated MGMT promotor,[12,13] and the previous retrospective study suggested that the overall and progression-free survival effect of morning administration is most profound in the methylated group,[5] we do not consider this finding as a signal requiring further attention. Furthermore, the clinical relevance of a prolongation in PFS from 3.5 to 5.3 months can be debated.

The observed increase in bone marrow toxicity among morning patients in our study is consistent across the CENTRIC and CORE trials and was also reported in the phase 2 trial that demonstrated the feasibility of

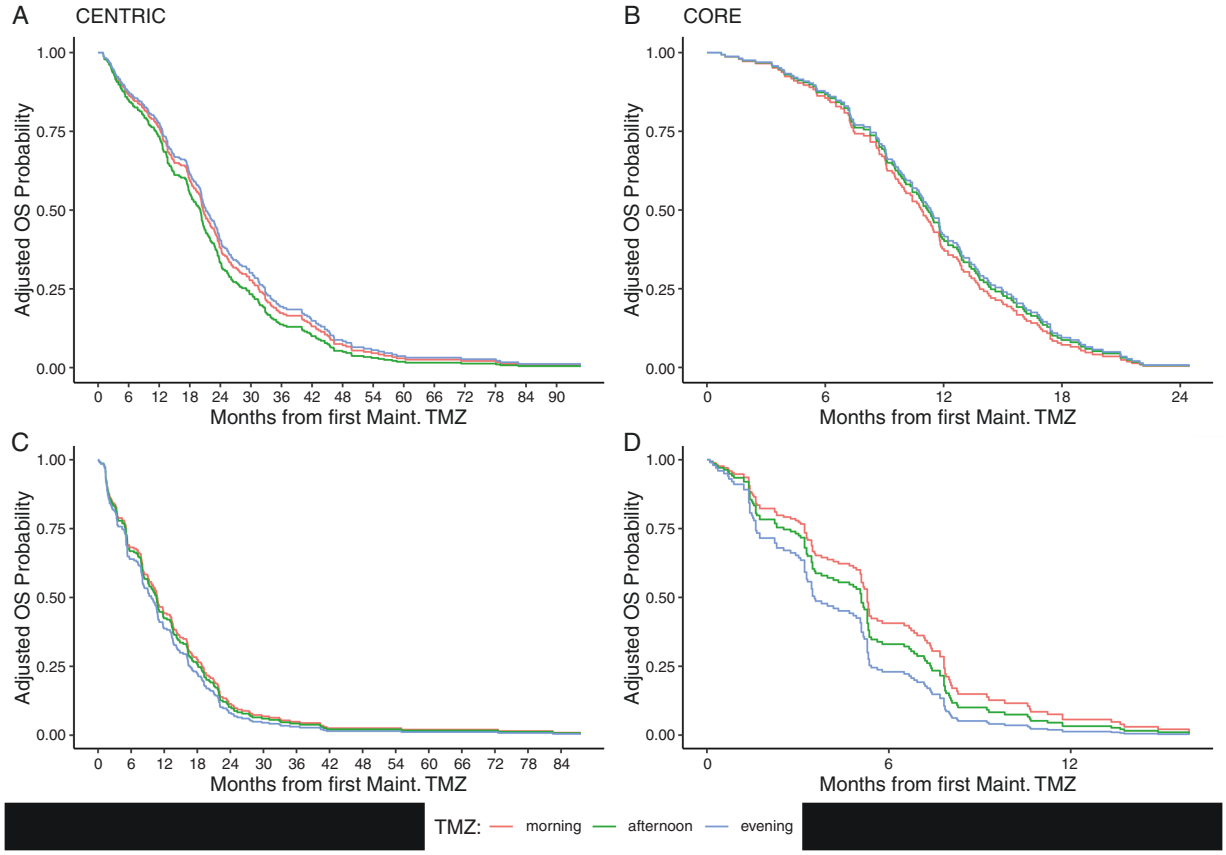

Figure 2. Adjusted Kaplan-Meier plots for overall survival (A and B) and progression-free survival (C and D) by administration time based on available data from maintenance therapy in CENTRIC (A and C) and CORE (B and D). Direct standardization[10,11] was used to adjust the survival curves. Please note: only data from deceased patients could be analyzed (see *Methods* section).

randomizing patients for morning or afternoon dosing.[6] The biological mechanism and potential clinical implications of this finding warrant further investigation, a causal relationship has not been proven.

Our data do not support the general assumption that taking TMZ in the evening reduces nausea. It is possible that we are not observing a causal relationship between the timing of administration and nausea, as patients who experience nausea may be advised to take their TMZ in the evening. Administration of antiemetics was at the local physicians discretion and no details recorded.

Limitations

Given the limitation to data from deceased patients only, this analysis might be significantly biased and does not yet exclude that timing of TMZ matters in patients most likely to derive benefit. The restriction to studying deceased patients only is a significant drawback, stemming from interpretation of EU legislation, which limits the ability to observe potential long-term survival benefits. Although patient confidentiality must be upheld, it should not come at the expense of hindering scientific progress and compromising patient care. We must strive to strike a balance that enables researchers to access and analyze clinical data effectively while ensuring the protection of patient privacy rights.

Apart from the survivorship bias, a further limitation of the study is that the time of TMZ administration was not randomized. The timing could be confounded by patient's preferences, clinical practice, or other unknown factors the statistical analysis has not adjusted for. The cutoff time between the administration groups is somewhat arbitrary. Furthermore, a single patient could have had TMZ administration both morning, afternoon, or evening. The time of TMZ intake has not diligently been recorded. Administration time may have been inconsistent throughout the treatment, and concomitant phase TMZ administration during RT has not been taken into consideration.

Patients included in clinical trials are a selected group of glioblastoma patients, this selection bias may hamper the generalizability of our findings.

Conclusion

Our post hoc analysis in newly diagnosed glioblastoma patients enrolled in two large prospective clinical trials does

Table 3. Number of Patients that Experienced AEs of Grades 1-3 or Higher Per TMZ Administration Time During Maintenance Phase. Either any AE, AE of Organ Class Gastrointestinal Disorders or Blood and Lymphatic System Disorders are Considered. For Each AE the Worst Grade Per Patient was Used. The Table is Based on the Restricted Dataset of Deceased Patients

	Morning, *N* = 102[a]	Afternoon, *N* = 123[a]	Evening, *N* = 35[a]
CENTRIC			
AEs of any kind			
Never	35 (34%)	43 (35%)	11 (31%)
Grades 1-2	27 (26%)	26 (21%)	6 (17%)
Grade 3 or higher	40 (39%)	54 (44%)	18 (51%)
AEs of gastrointestinal disorders			
Never	68 (67%)	69 (56%)	18 (51%)
Grades 1-2	32 (31%)	49 (40%)	16 (46%)
Grade 3 or higher	2 (2.0%)	5 (4.1%)	1 (2.9%)
AEs of blood and lymphatic system disorders			
Never	68 (67%)	94 (76%)	31 (89%)
Grades 1-2	15 (15%)	17 (14%)	0
Grade 3 or higher	19 (19%)	12 (9.8%)	4 (11%)
	Morning, *N* = 50[a]	Afternoon, *N* = 70[a]	Evening, *N* = 34[a]
CORE			
AEs of any kind			
Never	27 (54%)	27 (39%)	20 (59%)
Grades 1-2	19 (38%)	33 (47%)	12 (35%)
Grade 3 or higher	4 (8%)	10 (14%)	2 (5.9%)
AEs of gastrointestinal disorders			
Never	35 (70%)	48 (69%)	25 (74%)
Grades 1-2	15 (30%)	22 (31%)	9 (26%)
Grade 3 or higher	0	0	0
AEs of blood and lymphatic system disorders			
Never	38 (76%)	52 (74%)	33 (97%)
Grades 1-2	9 (18%)	11 (16%)	0
Grade 3 or higher	3 (6%)	7 (10%)	1 (2.9%)

[a] *n* (%).

not support the hypothesis that the timing of temozolomide administration during the maintenance phase offers a survival benefit. Our findings may aid in patient counseling and guide future research efforts.

We therefore consider prospective randomized clinical trial efforts on chronotherapy with TMZ during the maintenance phase of first-line treatment in a newly diagnosed glioblastoma patient with survival as an endpoint not justified at this time. However, our data suggest that bone marrow toxicity might occur less frequently when TMZ is administered in the evening compared to the morning.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice* (https://academic.oup.com/nop/).

Keywords

chronotherapy | glioblastoma | temozolomide

Funding

Not applicable.

Conflict of interest statement

MG: Grants or contracts from Evgen Pharm, Servier, LB: none, FK: none, BN: Patient care cost for the CORE clinical trial by MERC, consulting fees from AnHeart Scientific, Servier Advisory Board

Advisory Board, Patent for SR42127 HuR dimerization inhibitor submitted, chair of Data safety monitoring board of CNS Pharma, DR: Consulting fees for AnHeart Pharmaceuticals; Aptitude Health; BlueRock Therapeutics LP; CeCaVaGmbH & Co.KG; Chimeric Therapeutics; Elsevier; F. Hoffman La-Roche; Genenta Science; Inovio; Insightec; Janssen; Jupiter Life Sciences Consulting, LLC; Kintara; Kiyatec; Johnson & Johnson, Pharma; Lumanity; Menari Stemline; MGH Healthcare Holdings; Miltenyi Biomedicine GmbH; Neuvogen; Novocure; Paradigm Medical Communications; Putnam Inizii Associates, LLC; Sumitono Dainippon Pharma; Oncology; Triangle Insights Group; UCLA; UCSF; U of Minnesota; Vivacitas Oncology, Inc.; WebMD. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events for AnHeart Pharmaceuticals; Aptitude Health; BlueRock Therapeutics LP; CeCaVaGmbH & Co.KG; Chimeric Therapeutics; Elsevier; F. Hoffman La-Roche; Genenta Science; Inovio; Insightec; Janssen; Jupiter Life Sciences Consulting, LLC; Kintara; Kiyatec; Johnson & Johnson, Pharma; Lumanity; Menari Stemline; MGH Healthcare Holdings; Miltenyi Biomedicine GmbH; Neuvogen; Novocure; Paradigm Medical Communications; Putnam Inizii Associates, LLC; Sumitono Dainippon Pharma; Oncology; Triangle Insights Group; UCLA; UCSF; U of Minnesota; Vivacitas Oncology, Inc.; WebMD. Participation on a Data Safety Monitoring Board or Advisory Board for ImVax; CeCaVaGmbH; University of Pennsylvania. Stock or stock options fro AnHeart Therapeutics; Bionaut Labs, JCT: Research grants from novocure and Munich Surgical Instruments, Royalties from Spinger Publisher, and Honorarium for consultation from Novartis, Support from servier for attending meetings, leadership role in WFNS, RS: none, TG: none, MW: Grants or contracts from Novartis, Versameb, Quercis; Participation on a Data Safety Monitoring Board or Advisory Board for Curevac, Orbus, Philogen, MP: Consulting fees from Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape. MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, GLG, CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape.

Authorship statement

Concept and design: MG, MP; Analysis and interpretation: TG, LB, FK, MG, and MP; Writing of manuscript: MG, MP; Review and revision of the manuscript: LB, FK, BN, DR, JCT, RS, TG, and MW.

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Data availability

All data generated in this study are presented in this manuscript and supplementary materials or available upon reasonable request from the corresponding author

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